IN THE CLAIMS

Please amend Claims 26-27, 32-33, 38, 44, 48-52, 57-58, 62-65, 69, 73, 75, 77-78, 80, 82, 84-85, 87, 91-92, 94-96, 97-98, 102-104 as follows:

26. (twice amended) A mammalian host cell having [a modified] an endogenous target gene comprising a nucleotide regulatory [element] sequence which is: (a) different from the wild-type regulatory [element] sequence normally associated with the endogenous target gene, and (b) integrated, via homologous recombination, into the genome of the mammalian host cell [, so that the integrated regulatory element is operatively associated] in operative association with the endogenous target gene [of the mammalian host cell] so that the endogenous target gene coding sequence is not disrupted and expression of the endogenous target gene is controlled by the integrated regulatory [element] sequence.

27. (twice amended) The mammalian host cell of Claim 26 further having an amplifiable gene integrated into the host cell genome within or proximal to the endogenous target gene so that the endogenous target gene coding sequence is not disrupted and the [modified] endogenous target gene is also amplifiable.

Cancel Claims 28, 29, 30 and 31, without prejudice.

32. (twice amended) A mammalian host cell having an amplifiable gene integrated, via homologous recombination,

into the mammalian host cell genome within or proximal to an endogenous target gene of the host cell so that the endogenous target gene coding sequence is not disrupted and the endogenous target gene is also amplifiable.

C2 cont

33. (twice amended) The mammalian host cell of Claim 26, 27 or 32 [or 72] wherein the endogenous target gene contains at least one mutation introduced via [the] homologous recombination [of the exogenous amplifiable gene].

C3

38. (twice amended) The mammalian host cell of Claim 26, 27, or 32 [, or 72] wherein the mammalian host cell is a primate cell.

C4

44. (twice amended) A secondary expression host cell comprising a continuous cell line having the [modified] target gene of Claim 26, 27, or 32 [or 72].

C5

48. (twice amended) A method for producing a mammalian host cell having a [modified] endogenous target gene, comprising: (a) transforming a mammalian host cell with a nucleotide sequence comprising a nucleotide regulatory [element] sequence different from the wild-type regulatory sequence normally associated with the endogenous target gene, flanked by a nucleotide sequence homologous to a region of the host cell genome within or proximal to [an] the endogenous target gene [present in the mammalian host cell], so that the nucleotide regulatory [element] sequence is integrated via homologous recombination into the genome of the mammalian host

cell; and (b) selecting a transformed mammalian host cell [having the modified gene] in which the integrated nucleotide regulatory [element] sequence is operatively associated with the endogenous target gene, so that the endogenous target gene coding sequence is not disrupted and expression of the endogenous target gene is controlled by the integrated regulatory [element] sequence.

49. (twice amended) A method for producing a mammalian host cell having an amplifiable [modified] target gene, comprising:

(a) transforming a mammalian host cell with a nucleotide sequence comprising an amplifiable gene flanked by a nucleotide sequence homologous to a region of the host cell genome within or proximal to an endogenous target gene present in the mammalian host cell so that the amplifiable gene is integrated via homologous recombination into the genome of the mammalian host cell; and

(b) selecting a transformed mammalian host cell in which the amplifiable gene is integrated into the host cell genome within or proximal to the endogenous target gene so that the endogenous target gene coding sequence is not disrupted and the endogenous target gene is also amplifiable.

In Claim 50, first line, delete "49 or 76" and insert in its place -- or 49 --.

In Claim 51, first to second line, delete "49 or 76" and insert in its place -- or 49 --.

In Claim 52, first line, delete "49 or 76" and insert in its place -- or 49 --.

In Claim 57, first line, delete "49 or 76" and insert in its place -- or 49 --.

58. (amended) The method of Claim 48, 75 [,] or 49 [or 76] wherein the [exogenous] flanking homologous nucleotide [element] sequence introduces at least one mutation into the endogenous target gene upon integration via homologous recombination into the genome of the mammalian host cell.

62. (twice amended) A method for producing a secondary expression host cell which expresses a targeted gene, comprising:

(a) transforming a secondary expression host cell with nucleic acid encoding the [modified] targeted gene which was obtained from a mammalian host cell in which a nucleotide regulatory [element] sequence was integrated, via homologous recombination, into the genome of the mammalian host cell in operative association with an endogenous target gene of the mammalian host cell, so that the endogenous target gene coding sequence was not disrupted and expression of the endogenous target gene is controlled by the integrated regulatory [element] sequence; and

(b) selecting a transformed secondary host cell which expresses the [modified] targeted gene.

63. (twice amended) A method for producing a secondary <u>expression</u> host cell having an amplifiable [modified] <u>targeted</u> gene, comprising:

(a) transforming a secondary expression host cell with nucleic acid encoding the amplifiable [modified] <u>targeted</u> gene which was obtained from a mammalian host cell, in which the amplifiable gene was integrated, via homologous recombination, into the host cell genome within or proximal to an endogenous <u>target</u> gene so that <u>the endogenous target gene coding sequence was not disrupted and</u> [resulting modified] <u>the targeted</u> endogenous gene [is] <u>was</u> also amplifiable; and

(b) selecting a transformed secondary expression host cell which contains the integrated amplifiable gene and expresses the amplifiable [modified] <u>targeted</u> gene.

In Claim 64, first line, delete "63 or 83" and insert in its place -- or 63 --.

In Claim 65, first line, delete "63 or 83" and insert in its place -- or 63 --.

Cancel Claims 67 and 68, without prejudice.

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69. (amended) A method for producing a recombinant protein, comprising culturing a mammalian host cell having a [modified] <u>targeted</u> gene comprising a nucleotide regulatory [element] <u>sequence different from the wild-type regulatory sequence normally associated with the endogenous target gene,</u> integrated, via homologous recombination, into the genome of

the host cell in operative association with the [an] endogenous target gene of the mammalian host cell so that the endogenous target gene coding sequence is not disrupted and expression of the endogenous target gene is controlled by the integrated regulatory [element] sequence, under conditions wherein the [modified] targeted gene is expressed and the recombinant protein encoded by the [modified] targeted gene is produced.

Cancel Claim 72, without prejudice.

In Claim 73, second line, delete "72" and insert in its place -- 27 --.

75. (amended) The method of Claim 48 wherein the nucleotide sequence used to transform the mammalian host cell further contains an amplifiable gene which is integrated, via homologous recombination, into the host cell genome within or proximal to the endogenous target gene so that the endogenous target gene coding sequence is not disrupted and the endogenous target gene is also amplifiable.

Cancel Claim 76, without prejudice.

In Claim 77, first line, delete "76" and insert in its place -- 75 --.

In Claim 78, first line, delete "76" and insert in its place -- 75 --.

In Claim 80, first line, delete "49 or 76" and insert in its place -- or 49 --.

82. (amended) The method of Claim 62 in which the mammalian host cell further contains an amplifiable gene integrated [, via homologous recombination,] into the genome of the mammalian host cell within or proximal to [an] the endogenous target gene of the mammalian host cell, so that the endogenous target gene coding sequence is not disrupted and the endogenous target gene is also amplifiable.

Cancel Claim 83, without prejudice.

In Claim 84, first line, delete "83" and insert in its place -- 82 --.

In Claim 85, first line, delete "83" and insert in its place -- 82 --.

In Claim 87, first line, delete "63 or 83" and insert in its place -- or 63 --.

Cancel Claims 89 and 90, without prejudice.

91. (amended) The method of Claim 69 in which the mammalian host cell further has an amplifiable gene integrated, via homologous recombination, into the host cell genome within or proximal to the endogenous target gene so that the endogenous target gene coding sequence is not

disrupted and the [resulting modified] endogenous target gene is also amplifiable, and the culturing is performed under conditions wherein the [modified] targeted gene is amplified.

92. (amended) A method for producing a recombinant protein, comprising culturing a mammalian host cell in which an amplifiable gene was integrated, via homologous recombination, into the genome of the host cell within or proximal to an endogenous target gene of the host cell, so that the endogenous target gene coding sequence is not disrupted and the endogenous target gene is also amplifiable, under conditions which amplify both the amplifiable gene and the endogenous target gene, so that expression of the recombinant protein encoded by the endogenous target gene is enhanced.

Cancel Claim 93, without prejudice.

In Claim 94, first, line, delete "92 or 93" and insert in its place -- 69, 91 or 92 --.

In Claim 95, first line, delete "93" and insert in its place -- 91 --.

In Claim 95, second line, delete "element" and insert in its place -- sequence --.

In Claim 96, first line, delete "93" and insert in its place -- 91 --.

In Claim 96, second line, delete "element" and insert in its place -- sequence --.

97. (amended) A method for producing a recombinant protein, comprising culturing a secondary expression host cell having a [modified] targeted gene obtained from a mammalian host cell in which a nucleotide regulatory [element] sequence was integrated, via homologous recombination, into the genome of the mammalian host cell in operative association with an endogenous target gene of the mammalian host cell so that the endogenous target gene coding sequence was not disrupted and expression of the endogenous gene is controlled by the integrated regulatory [element] sequence, under conditions wherein the [modified] targeted gene is expressed and the recombinant protein encoded by the [modified] targeted gene is produced.

C 12

98. (amended) The method of claim 97 in which the secondary expression host cell further has an [integrated] amplifiable gene [operatively associated with the modified gene], integrated within or proximal to the target gene so that the target gene coding sequence is not disrupted and the targeted gene is also amplifiable, and the culturing is performed under conditions wherein the [modified] targeted gene is amplified and expression of the recombinant protein is enhanced.

Cancel Claim 99, without prejudice.

100. (new) A method for producing a recombinant protein, comprising culturing a secondary expression host cell having a [modified] targeted gene derived from a mammalian host cell in which an amplifiable gene was integrated, via homologous recombination, into the genome of the mammalian host cell within or proximal to an endogenous gene of the mammalian host cell so that the target gene coding sequence is not disrupted and the resulting [modified] targeted gene is also amplifiable, under conditions wherein the [modified] targeted gene is amplified and expression of the recombinant protein is enhanced.

Cancel Claim 101, without prejudice.

In Claim 102, first line, delete "100 or 101" and insert in its place -- 97, 98 or 100 --.

In Claim 103, first line, delete "101" and insert in its place -- 98 --.

In Claim 104, first line, delete "101" and insert in its place -- 98 --.

REMARKS

The Applicants take this opportunity to thank the Examiner, her supervisors and directors for the interview which was courteously conducted on November 16, 1994 (hereinafter referred to as "the Interview").